IN THE CLAIMS

Please amend claims 1 and 5 as indicated in Appendices A and B submitted herewith. Appendix A is a marked-up copy of the amended claims and Appendix B is a clean copy of the amended claims.

REMARKS

Claims 1-8 are currently pending in the present application. The claims have been amended in the expectation that the amendments will place this application in condition for allowance. The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Informalities Noted by the Examiner

The Official Action states tat various informalities have been noticed by the Examiner. Applicants have amended the specification of the present application to correct the informalities noted by the Examiner. These amendments do not add new matter to the instant application. In particular, the subject matter of Table 1 may be inferred from Figs. 2B, 3A, and [illegible] of Table 2 may be inferred from Fig. 4 and Example 3. The subject matter of the insertion on page 14 may be inferred from Fig. 5. The other corrections are of obvious typographical errors.

2. Rejection of Claims 1-8 under 35 U.S.C. § 112, 1st paragraph

The Official Action states that claims 1-8 are rejected under

35 U.S.C. § 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

Applicants respectfully traverse this rejection. In order to make an enablement rejection, the Examiner has the initial burden to establish a *reasonable* basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). The test under 35 U.S.C. § 112, first paragraph, for determining compliance with the enablement requirement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988).

Applicants respectfully assert that a person skilled in the art of molecular genetics, the subject matter of the presently pending claims, would be able to carry out the invention as defined in the presently pending claims on the basis of the information provided in the instant specification.

In particular, the instant specification provides specific information regarding 2 different diseases which can be treated according to the presently claimed invention, i.e., cystic fibrosis (CF) and spinal muscular atrophy (SMA) (see page 16,

lines 22-29); 3 different types of cells, i.e., COS-1 (monkey), HeLa (human), and an epithelial cell line established from a nasal polyp sample of a CF patient (see page 10, lines 1-13 and page 15, lines 15-22); and 7 different ASFs, i.e., ASF/SF2, hnRNPA1, E4-ORF3, E4-ORF6, SRp20, Sc35, and Htra2-β1 (see Figs. 6 and 7). Accordingly, the instant disclosure is in compliance with the statute. A person of ordinary skill in the art would understand how to make and use the present invention based on the teachings present in the specification.

Additionally, applicants note that those of skill in the art have subsequently succeeded in investigating various modes of treatment of diseases involving abnormal expression of genes caused by aberrant splicing in cells. The Examiner's attention in this regard is directed to Nissim-Rafinia, M. and Kerem, B. (2002) *TRENDS in Genetics*, 18: 123-127, particularly page 126, bottom of left-hand column and right hand column. Likewise, the Examiner's attention is further directed to Nakai, K. and Sakamoto, H. (1994) *Gene*, 141(2): 171-177 which reports construction of a database caused by aberrant splicing of genes. Courtesy copies of these references are enclosed for the Examiner's review.

Lastly, applicants respectfully submit herewith a Declaration under 37 C.F.R. 1.132 by Prof. Hermona Soreq, a Professor of Molecular Biology in the Department of Biological

Chemistry and Vice Dean for R&D in the Faculty of Science of the Hebrew University of Jerusalem, Israel. Prof. Soreq declares that "diseases caused by aberrant splicing", i.e., the presently claimed disease, is a known definition of disease that enables any person skilled in the art to perform a simple search and identify the diseases to be caused by aberrant splicing. Likewise, Prof. Soreq notes ASFs are a well-defined concept known to those skilled in the art. Accordingly, Prof. Soreq declares that a person skilled in the art would know, based on the instant specification, how to identify diseases caused by aberrant splicing and appropriate ASFs as well as how to use them in the treatment of disease. This 132 Declaration, then, provides additional post-filing evidence that a person of ordinary skill in the art would find the presently claimed invention enabled by the instant specification. *See In re Brana*, 51 F.3d 1560, 1561 (Fed. Cir. 1995).

In view of the information provided in the instant application, the level of knowledge to those skilled in the art as evidenced by the attached articles, and the attached 132 Declaration, it is respectfully submitted the identity of the types of diseases which may be treated according to the presently claimed invention, the identity of the agonists of ASFs, and the treating condition for administering an ASF would be known to those of skill in the art.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 1-8.

3. Rejection of Claims 1-8 under 35 U.S.C. § 112, 1st paragraph

The Official Action states that claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse this rejection. The test under 35 U.S.C. 112, first paragraph, for determining compliance with the written description requirement is whether the application clearly conveys that an applicant has invented the subject matter which is claimed. *In re Barker*, 194 U.S.P.Q. 470, 473 (C.C.P.A. 1977). Also, the applicant must convey to the public what the applicant claims as the invention so that the public may ascertain if the patent applicant claims anything in common use or already known. MPEP 2163. [illegible] specification must convey that the applicant was in possession of the invention. MPEP 2163. The Examiner is respectfully reminded that the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 191 U.S.P.Q. 90, 98 (C.C.P.A. 1976).

As noted by the Examiner, the instant specification demonstrates the effect of overexpression of DNA sequences encoding ASF proteins on aberrant splicing. However, this overexpression results in the production of the ASF protein product to the cell.

The Examiner is reminded that applicants are not required to describe each and every alternative and possibility in order to show that the inventor had possession of the presently claimed invention. *In re Ruschig*, 154 U.S.P.Q. 118, 123 (C.C.P.A. 1967). The present specification provides a sufficient number of examples (Examples 1-5) to indicate possession of the invention at the time the invention was filed.

Additionally, applicants respectfully submit herewith a Declaration under 37 C.F.R. 1.132 by the present inventor. This Declaration demonstrates that on the basis of the description in the instant specification, a person skilled in the art would understand the full scope of the invention and know how to use ASFs for the treatment of diseases by restoring gene function. The Examiner is reminded an opinion declaration, such as this one, is proper in addressing a written description rejection. *In re Alton*, 27 U.S.P.Q.2d 1578, 1583 (Fed. Cir. 1996).

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 1-8.

4. Rejection of Claims 1-8 under 35 U.S.C. § 112, 2d paragraph

The Official Action states that claims 1-8 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully traverse this rejection. Regarding the 112, second paragraph rejection, caselaw has defined two requirements under the statute: (1) whether the applicant has stated the invention as something elsewhere in the application which would not fall under the scope of the claims; and (2) whether the claims would be communicated with a reasonable degree of particularity and distinctness to a person skilled in the art in light of the content of the disclosure and the teachings of the prior art. MPEP 2171, 2173, and 2173.02.

Applicants thank the Examiner for her suggestions regarding the claims. Accordingly, applicants have amended claim 1 to include the step of [illegible] the disease and claim 5 to include the full spelled out name for the "SR protein".

Regarding the term "a disease", this term is defined in claim 1 as "resulting from an abnormal expression of genes caused by aberrant splicing in cells". Applicants respectfully assert that this term is clearly defined and would be understood by a person skilled in the art.

Regarding the term "abnormal expression of genes",

applicants submit this term is clearly defined in the instant specification on page 4, lines 12-21. It is clear from this definition what genes are intended.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 1-8.

CONCLUSION

Claims 1-8 are currently pending in the present application. Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejections and allow all pending claims herein.

Respectfully submitted,
NATH & ASSOCIATES PLLC

Date: 4 Feb 03

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PATENT

Attorney Docket No. 24020-X

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

KEREM

Serial No: 09/871,809 Examiner: C. Kam

Filed: July 5, 2000 Art Unit: 1653

For: **CONTROL OF GENE EXPRESSION**

Appendix A

Please amend the following claims as indicated in the following marked up copy of the claims.

1. (Once Amended) A method of treatment of an individual suffering from a genetic disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, the method comprising:

Administering to said cells of the individual or to tissue or organs of said individual comprising said cells, an effective amount of an alternative splicing factor (ASF), wherein abnormal expression shifts towards normal expression of the gene thereby treating said disease.

5. (Once Amended) A method according to claim 1, wherein the ASF is selected from the group consisting of:

(i) a member of the serine/arginine-rich (SR) protein;

(ii) heterogeneous nuclear ribonucleoprotein A1;

(iii) viral factor E4-ORF3;

(iv) viral factor E4-ORF6; and

(v) an agonist of any one of (i) to (iv).

PATENT

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For: **CONTROL OF GENE EXPRESSION**

Appendix B

Please amend the following claims as indicated in the following clean copy of the claims.

A1

1. (Once Amended) A method of treatment of an individual suffering from a genetic disease resulting from an abnormal expression of genes caused by aberrant splicing in cells, the method comprising:

Administering to said cells of the individual or to tissue or organs of said individual comprising said cells, an effective amount of an alternative splicing factor (ASF), wherein abnormal expression shifts towards normal expression of the gene thereby treating said disease.

A2

5. (Once Amended) A method according to claim 1, wherein the ASF is selected from the group consisting of:

(i) a member of the serine/arginine-rich (SR) protein;

(ii) heterogeneous nuclear ribonucleoprotein A1;

(iii) viral factor E4-ORF3;

(iv) viral factor E4-ORF6; and

(v) an agonist of any one of (i) to (iv).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

KEREM

Serial No: 09/871,809 Examiner: C. Kam

Filed: July 5, 2000 Art Unit: 1653

For: **CONTROL OF GENE EXPRESSION**

Appendix C

Please amend the instant specification as indicated in the following marked up copy of the specification.

Please amend the specification by replacing the paragraph on page 4, lines 8-11 with the following:

--The term "*treatment*" in the context of the present invention does not necessarily mean complete curing of the disease, but may also refer to [elevation] elimination of some of the undesired effects of the disease, or prevention of the most serious effects before they are manifested in the individual.--

Please amend the specification by replacing the paragraph on page 5, lines 1-7 with the following:

--The method of the invention concerns administering to said cells, or tissues or organs comprising said cells, as will be

explained hereinbelow, an effective amount of an alternative splicing factor, (ASF) i.e. any factor which is known to modulate alternative splicing, for example, those mentioned in the publications referred to in the list of references, such as members of the serine/arginine (SR) protein family including the SF2/ASF and its antagonists, as well as the heterogenous nuclear ribonucleoprotein A1 (hnRNP A1).--

Please amend the specification by replacing the paragraph on page 10, line 30 with the following:

--19i5 5' GCCCGACAAATAACCAAGTGA3' SEQ ID NO. 1--

Please amend the specification by replacing the paragraph on page 11, lines 1-4 with the following:

--specific for intron 19 of the CFTR gene and X20 5' ATCCAGTTCTTCCCAAGAGGC 3' SEQ ID NO. 2 specific for exon 20. X20 was fluorescently labeled with 6-FAM. The PCR products of the correctly and aberrantly spliced [illegible] bp, respectively.--

Please amend the specification by replacing the paragraph on page 11, line 7 with the following:

--8Ri5 5' TGCATTAATGCTATTCTGATTC 3' SEQ ID NO. 3--

Please amend the specification by replacing the paragraph on page 11, lines 8-11 with the following:

--specific for intron 8 of the CFTR gene and F10Rx3 5′ TTGGCATGCTTTGATGACGC 3′ SEQ ID NO. 4 specific for exon 10 (shown in Fig. 1b). F10Rx3 was fluorescently labeled with 6-FAM. The PCR products of the correctly and aberrantly spliced transcripts were 513 and 330 bp, respectively.--

Please amend the specification by replacing the paragraph on page 12, lines 5-6 with the following:

--pCG 5′UTR: GACGCCATCCACGCTGTT SEQ ID NO. 5, which is specific for the 5′ untranslated region (UTR) derived from the pCG vector, and--

Please amend the specification by replacing the paragraph on page 12, lines 7-8 with the following:

--A1exp-5′: AAAGTCTCTCTTCACCCTGC SEQ ID NO. 6, which is specific for the 5′ UTR of the endogenous [illegible] were used as forward primers, and--

Please amend the specification by replacing the paragraph on page 12, lines 9-11 with the following:

--A1exp-3′: AAGTGGGCACCTGGTCTTTG SEQ ID NO. 7 was used as a reverse primer. All three hnRNP A1 primers were present in the

same reaction. The primers used for E4-ORF6 analysis were:--

Please amend the specification by replacing the paragraph on page 12, line 12 with the following:

--ORF6exp-5': CCCGAATGTAACACTTTGAC SEQ ID NO. 8 as a forward primer, and--

Please amend the specification by replacing the paragraph on page 12, line 13 with the following:

--ORF6exp-3': CGGTACCATATAAACCTCTG SEQ ID NO. 9 as a reverse primer.--

Please amend the specification by replacing the paragraph on page 12, lines 20-29 with the following:

--CFTR containing genomic sequences from exon 19, the cryptic 84 bp exon, exon 20 and their upstream and downstream flanking sequences were introduced into the pSI expression vector (Fig. 1a). The minigenes containing [illegible] (p3849M) or the normal sequence (p3949N) were transfected into HeLa and COS-1 cells. Both minigenes were successfully expressed and spliced in these cells (Fig. 2 and Table 1). All the spliced transcripts from P3849M included the cryptic "*84 bp exon*" (486 bp RT-PCR product in Fig. 2). No correctly spliced transcripts were detected from this minigene, All the

transcripts produced from [p3949M] p3949N were correctly spliced (402 by RT-PCR product in Fig. 2), thus, the 84 bp in this minigene were not recognized as an exon.--

Please amend the specification by replacing the paragraph on page 14, lines 15-25 with the following:

--It has been hypothesized that upon infection by adenovirus, and expression of its splicing factors, the cellular splicing activity might be affected and thus the splicing pattern of CFTR transcripts carrying splicing mutations might be modified. In order to test this hypothesis the effect of one of the adenoviral splicing factors, E4-ORF6, was known to have a similar activity to hnRNP A1. Transient cotransfection into both COS-1 and HeLa cells of p3849M and the adenovirus E4-ORF6 cDNA (pCMVE4-ORF6) (5 or 10 µg) generated correctly spliced transcripts (Fig. 5). In repeated experiments 9% of total p3849M RNA in COS-1 cells, and 8% in HeLa cells were correctly spliced (Fig. 5a and Table 2). [illegible] infection of the p3849N and pCMVE4-ORF6 into COS-1 cells, no effect on the splicing pattern of the minigene was found, as expected for a minigene with the normal sequence. In each experiment the expression of transfected pCMVE4-ORF6 was verified by RT-PCR analysis (Fig. 5b).--

Please amend the specification by replacing the paragraph on page 15, line 26 to page 16, line 7 with the following:

--Transient transfections of 091398k cells with cellular factors were performed, using DAC-30. The use of DAC-30 resulted in transfection efficiency of ~60%. In these experiments splicing factors were analyzed that were shown to affect the splicing ~~pattern of minigene carrying the splicing mutations: ASF/SF2,~~ hnRNPA1, E4-ORF3 and E4-ORF6. The results showed that all these factors modulated the splicing pattern of CFTR transcripts (Fig. 6). The ASF/SF2, hnRNP A1 and E4ORF6 promoted exon skipping and led to a decrease in the level of aberrantly spliced transcripts **[**(Fig. 7)**]** (Fig. 6). The most significant effect was achieved with ASF/SF2 which led to a decrease of the aberrantly spliced transcripts from 21% to 11%. The viral factor E4-oRF3 slightly promoted exon inclusion and led to an increase in the level of aberrantly spliced transcripts (21% to 28%). Thus, the mean effect could have reached ~35%.--

Please amend the specification by inserting the following paragraphs and tables on page 17, line 5:

--Table 1.

Levels of Correctly Spliced p3849N and p3849M Transcripts (%)

	COS-1	HeLa
p3849N	100	100
p3849M	0	0
p3849M+A1	12±3	No A1 exp.
P3849M+ORF6	9±3	8±3

Table 2.

Levels of Aberrantly Spliced p5T and p9T Transcripts (%) in COS-1 cells

	-A1	+A1
p5T	24±8	44±12
p9T	3±2	4±3

--

PATENT

Attorney Docket No. 24020-X

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KEREM

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Filed: July 5, 2000 Art Unit: 1653

For: **CONTROL OF GENE EXPRESSION**

Appendix D

Please amend the instant specification as indicated in the following clean copy of the specification.

Please amend the specification by replacing the paragraph on page 4, lines 8-11 with the following:

--The term "*treatment*" in the context of the present invention does not necessarily mean complete curing of the disease, but may also refer to elimination of some of the undesired effects of the disease, or prevention of the most serious effects before they are manifested in the individual.--

Please amend the specification by replacing the paragraph on page 5, lines 1-7 with the following:

--The method of the invention concerns administering to said cells, or tissues or organs comprising said cells, as will be

explained hereinbelow, an effective amount of an alternative splicing factor, (ASF) i.e. any factor which is known to modulate alternative splicing, for example, those mentioned in the publications referred to in the list of references, such as members of the serine/arginine (SR) protein family including the SF2/ASF and its antagonists, as well as the heterogenous nuclear ribonucleoprotein A1 (hnRNP A1).

Please amend the specification by replacing the paragraph on page 10, line 30 with the following:

--19i5 5' GCCCGACAAATAACCAAGTGA3' SEQ ID NO. 1--

Please amend the specification by replacing the paragraph on page 11, lines 1-4 with the following:

--specific for intron 19 of the CFTR gene and X20 5' ATCCAGTTCTTCCCAAGAGGC 3' SEQ ID NO. 2 specific for exon 20. X20 was fluorescently labeled with 6-FAM. The PCR products of the correctly and aberrantly spliced transcripts were 402 and 366 bp, respectively.--

Please amend the specification by replacing the paragraph on page 11, line 7 with the following:

--8Ri5 5' TGCATTAATGCTATTCTGATTC 3' SEQ ID NO. 3--

Please amend the specification by replacing the paragraph on page 11, lines 8-11 with the following:

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Please amend the specification by replacing the paragraph on page 12, lines 5-6 with the following:

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Please amend the specification by replacing the paragraph on page 12, lines 7-8 with the following:

--A1exp-5': AAAGTCTCTCTTCACCCTGC SEQ ID NO. 6, which is specific for the 5' UTR of the endogenous hnRNP A1 gene, both of which were used as forward primers, and--

Please amend the specification by replacing the paragraph on page 12, lines 9-11 with the following:

--A1exp-3': AAGTGGGCACCTGGTCTTTG SEQ ID NO. 7 was used as a reverse primer. All three hnRNP A1 primers were present in the

same reaction. The primers used for E4-ORF6 analysis were:--

Please amend the specification by replacing the paragraph on page 12, line 12 with the following:

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--CFTR containing genomic sequences from exon 19, the cryptic 84 bp exon, exon 20 and their upstream and downstream flanking sequences were introduced into the pSI expression vector (Fig. [illegible] (p3849M) or the normal sequence (p3949N) were transfected into HeLa and COS-1 cells. Both minigenes were successfully expressed and spliced in these cells (Fig. 2 and Table 1). All the spliced transcripts from P3849M included the cryptic "*84 bp exon*" (486 bp RT-PCR product in Fig. 2). No correctly spliced transcripts were detected from this minigene. All the

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Please amend the specification by replacing the paragraph on page 14, lines 15-25 with the following:

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Please amend the specification by replacing the paragraph on page 15, line 26 to page 16, line 7 with the following:

--Transient transfections of 091398k cells with cellular factors were performed, using DAC-30. The use of DAC-30 resulted in transfection efficiency of ~60%. In these experiments splicing factors were analyzed that were shown to affect the splicing pattern of minigene carrying the splicing mutations: ASF/SF2, hnRNPA1, E4-ORF3 and E4-ORF6. The results showed that all these factors modulated the splicing pattern of CFTR transcripts (Fig. 6). The ASF/SF2, hnRNP A1 and E4ORF6 promoted exon skipping and led to a decrease in the level of aberrantly spliced transcripts (Fig. 6). The most significant effect was achieved with ASF/SF2 which led to a decrease of the aberrantly spliced transcripts from 21% to 11%. The viral factor E4-oRF3 slightly promoted exon inclusion and led to an increase in the level of aberrantly spliced transcripts (21% to 28%). Thus, the mean effect could have reached ~35%.--

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	-A1	+A1
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